REMARKS/ARGUMENTS

Reconsideration of the above-identified application respectfully requested.

Claim Amendments

The instructive office action that clarified the basis for rejections is noted. The claims are amended accordingly.

Claim 35, replacing independent claim 22, is directed to a kit to provide an individual or personalized treatment of suramin to a patient based on said patient's own unique characteristics. Claim 35 provides a functional relationship between the printed matter and a substrate, which now is present in a defined amount. Claim 35 does not list a composition of suramin and other cytotoxic agents. The idea of an individual or personalized nomogram is disclosed in the application, for example, at p. 6, ll. 16-21; p. 12, ll. 22-25; and p. 24, ll. 13-16.

Several dependent claims also have been cancelled. Other claims have been amended due to new claim 35. No new matter is added; thus, entry of the claim amendments respectfully is requested.

Claim Rejection under 35 U.S.C. § 101

Claims 32-34 are rejected under 35 USC §101 because the claimed invention is directed to non-statutory subject matter by virtue of "active method steps" being recited. Claims 32 and 33 have been amended to remove the offending language, while claim 34 has been cancelled. Withdrawal of this ground of rejection, then, respectfully is requested.

Claim Rejection under 35 U.S.C. § 112 – 2nd paragraph

Claims 22, 26-28, and 32-34 are rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The term lacking antecedent basis has been deleted. Withdrawal of this ground of rejection, then, respectfully is requested.

Claim Rejections under 35 U,S,C, § 103(a)

Claims 22, 26-28, and 32-34 are rejected as being unpatentable over Agyin.

Claims 22, 27-28, and 32-34 are rejected as being unpatentable over Tu *et al.* in view of Agyin.

Claims 22, 26-28, and 32-34 are rejected over Lopez *et al.* in view of Klohs, and Agyin, Lopez.

New claim 35 is directed to a kit for providing personalized or individual treatment of suramin to a patient such that the printed matter breathes "life and meaning" to the substrate suramin and enables using suramin in a personalized manner. Such use and personalized treatment according to a patient's characteristics (squared value of body surface area and treatment time status) are not disclosed in Agyin. Further, claim 35 lists suramin as the only substrate in the kit and in a defined amount (or quantity), where the intended use of suramin as a personalized treatment is achieved by using the specified dosing nomogram. Neither Agyin. Klohs, or Lopez disclose a product or a kit comprising a defined amount of suramin as the substrate given in accordance with the nomogram (instructions).

Claims 22, 26-28, and 32-34 also are rejected as the targeted plasma suramin concentration of below 200 μM has been anticipated by Tu, Klohs, *or* Lopez. The Examiner's attention is drawn to a number of differences between this prior art and the personalized dosing nomogram in the instant disclosure. First, the prior art does <u>not</u> teach the personalized dosing nomogram or the equations of claim 35.

Second, the prior art teaches the use of suramin as a cytotoxic agent at the maximally tolerated doses that produce toxicity, *e.g.*, hematologic and gastrointestinal toxicity, in patients (plasma or serum concentration of over 100 μg/ml). For example, Tu describes using suramin at doses that produced the maximum tolerated steady state plasma concentration of 150-200 μg/ml, maintained for up to 45 weeks, when combined with doxorubicin. Klohs states, *inter alia*:

> Ideally, suramin will be administered at a dose which will produce plasma levels of about 100 to about 300 μg/ml. Suramin typically is administered by intravenous infusion over a 12- to 16-week period, as needed to maintain the indicated plasma levels. Suramin will be administered at about the same dose levels and frequency according to this invention.
>
> Klohs @ col. 2, ll. 34-38.

Hence, both Tu and Klohs are teaching the artisan to maintain the noted plasma levels (*viz.*, 100 to 300 μg/ml) for an extended time period of, *e.g.*, 12 to 16 weeks.

Lopez teaches using suramin in a culture flask and does not teach the determination of the suramin dose in a subject.

In contrast, the instant disclosure teaches the determination of the suramin dose that would yield and maintain low and non-cytotoxic plasma concentrations of 90 μg/ml or less for the duration of presence of effective chemotherapy concentrations, *e.g.*, 48 hours. As further discussed below, the suramin dose depends on the targeted plasma concentrations. In addition, the elimination of suramin at low doses is more rapid than at high doses (see instant

application, page 5, line 20 *et seq*.). Hence, the method applied in the prior art cannot be used to determine the suramin dose needed for personalizing the suramin treatment in a patient according to said patient's characteristics.

Third, neither Tu nor Klohs contains the enablement steps to determine the suramin dose that would yield the targeted plasma concentrations. For example, Tu describes the method of suramin dose determination as follows:

> Suramin was delivered iv over 2 h on Mondays and/or Thursdays. All patients received a test dose of 200 mg of suramin followed by a loading dose of 1 g/m^2. Subsequent suramin boluses were based on suramin concentrations measured 24 h after the previous infusion of the drug (i.e. on Tuesdays and Fridays). Suramin doses were estimated manually by the treating physician after a loading dose and two additional doses had been administered. Suramin doses were adjusted proportionately based on the assessment of Cpss.
>
> Tu @ p. 1194, under "Treatment Plan".

This instruction is <u>not</u> enabling, as it is unclear in its meaning. The required dose is "estimated manually", but the method of estimation is <u>not</u> detailed, as the meaning of "assessment of Cpss" is uncertain. For example, is the Cpss assumed to be equal to the plasma concentration measured one day after the last administered dose? Or is continuous accumulation of suramin concentrations taken into account? Due to the unusually long half-life of suramin ranging from greater than 11 days to as long as 78 days (see instant application, Table 3), achievement of steady-state concentrations is not expected after "a loading dose and two additional doses", or approximately 7 days at the biweekly dosing schedule. The standard assumption in clinical pharmacokinetics is that 3-4 half-lives are required to approach steady state, which would be at least 33 days for suramin. If the continuous accumulation of suramin concentrations is taken into account, is a one-compartment pharmacokinetic model assumed, or a two-compartment or a three-compartment model? Since all these factors have not been discussed, the methodology is unclear and not enabling.

Fourth, the method of Tu requires using a test dose in a patient in conjunction with repeated plasma sampling and real time drug concentration analyses for approximately 7 days, in order to calculate the dose that is eventually given to the same said patient. Clearly, then, the method of Tu requires <u>delaying</u> the first drug treatment until the concentration analyses are completed. In contrast, the instant disclose does not require the use of a test dose and can be used to instantaneously determine the first treatment dose.

Fifth, the method of Tu requires concentration analysis of suramin in blood samples of the patient. In contrast, the nomogram does not require analyzing the suramin concentration in multiple blood samples from a patient in order to calculate the dose. The nomogram disclosed in the instant application is a simple and practical way to calculate a suramin dose in individual patients based on the easily obtained patient characteristics, such as, squared value of said patient's body surface area and said patient's treatment time status.

Sixth, the prior art does not offer personalized treatment based on the treatment time status of an individual patient, which, as indicated below, is required to use the substrate in the current kit to achieve its intended therapeutic purpose. In contrast, the instant disclosure accommodates changes in dosing intervals, a frequent necessity in clinical practice.

The Examiner further noted MPEP § 2112.01 and established case law that indicates the requirement of "new and unobvious functional relationship between the printed matter and the substrate". Applicants submit that the product described in new claim 35 satisfies the requirement of a functional relationship between the printed matter and the claimed substrate (*viz.*, suramin).

Applicants respectfully draw Examiner's attention to the following surprising features and unobviousness of the instant disclosure. For most drugs, choosing the proper dose is a relatively routine and easy task. For example, most chemotherapy agents are given at a fixed frequency and at a fixed dose, because most agents have plasma half-lives of several hours and are eliminated from the body within days. Therefore, most agents will not show significant accumulation in the body by the time the next dose is administered, which usually is in 7 or 21 days. However, this general practice does <u>not</u> apply to suramin, due to its unusual pharmacokinetic characteristics.

First, the disposition of low and non-cytotoxic doses of suramin in patients shows a substantial inter-subject variability (180%), indicating that the same dose of suramin will <u>not</u> result in the same, desired plasma concentration in all patients. In fact, different patients require doses of up to 5-fold different size (Chen *et al.*, *Pharm. Res.*, 23, 1265, 2006).

Second, suramin has an unusually slow elimination from the body with a half-life exceeding 11 days, which means a significant residual amount will remain in the body at the time of the next treatment (*e.g.*, about 25% of the dose remaining in 20 days for a half-life of 10 days).

Third, the fixed dosing schedules taught in the prior art, *e.g.*, Tu, for maintaining constant and high plasma concentrations over 100 μM for over more than two months were derived from studies in male patients with prostate cancer. It is uncertain whether these schedules can be

used in female patients in view of the gender-dependent differences in suramin pharmacokinetics as discovered by Applicants (see Example IV in the instant application).

Fourth, unexpected changes in treatment frequency or time intervals between treatment cycles are fairly common in cancer chemotherapy. These changes will affect the amount of residual drug and, therefore, introduce uncertainty on deciding on the proper dose. For example, if the dose in the subsequent treatment exceeds the amount that has been eliminated, drug accumulation will occur and will cause the plasma concentrations to increase, *e.g.*, to levels where suramin is not effective. Conversely, an insufficient dose will yield ineffective concentrations. Hence, the instant disclosure of a kit to take into account the time interval between treatments for calculating the personalized suramin dose is absolutely required to achieve the benefits of suramin sensitization. In short, the surprising findings of the unusual and unexpected pharmacokinetics of suramin in human patients, in view of the multiple sources of inter-patient variability means that, absent the dosing nomogram in the instant disclosure, it will be **impossible** to predict how an individual patient will react to the administered dose of the suramin.

Applicants further offer the following discussion to highlight the unobviousness and novelty in the instant disclosure. As indicated in the application and in Applicants' publication (Chen, 2006), the development and validation of the nomogram method required extensive research, and yielded surprising and unexpected results that either cannot be anticipated from the prior art, or contradicts the prior art. The nomogram development was a multi-step process, as stated in Chen, *et al.*:

> First, we used the pharmacokinetics results in the first cohort of six phase I patients to determine the duration that covered >90% of paclitaxel/carboplatin AUC, with the goal of maintaining the plasma suramin concentrations at between 10 and 50 μM over this duration. This led to adjustments in the suramin regimen; administering suramin in two split doses yielded the target concentrations over 48 hour in the second cohort of six patients. The pharmacokinetics results of these 12 patients were then used with PPK [population-based pharmacokinetic] analysis to derive suramin dosing equations, which were then used to predict the dose in three additional patients. Through retrospective and prospective analyses of the precision and accuracy of the PPK based dosing equations, a correction factor was identified and used to derive a dosing nomogram. The predictive power of the nomogram was evaluated in 47 phase II patients.
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> Chen, *et al.* (2006), page 1266: 2, last ¶.

As described in the application (Example IV), during the PPK phase of the nomogram development, 10 potential covariates were evaluated. One of these was patient gender. The

initial results in a small number of patients suggested that the dose was affected by patient gender. However, further evaluation in large numbers of patients indicated that the gender-related difference in dose requirement was so small that it could be ignored. Another potential covariate was creatinine clearance, which was expected to be strongly correlated with suramin clearance. This is because earlier reports indicated renal elimination as the primary route of clearance of suramin. During further evaluation, Applicants discovered that creatinine clearance was not a significant predictor of PPK parameters. Applicants investigated this apparent discrepancy in a study in 38 patients, and determined that the renal clearance of non-cytotoxic suramin in human patients was surprisingly low, accounting for only approximately 10% of the total clearance.

Another surprising finding was that body surface area (BSA) was a less accurate predictor of dose requirement than its squared value: BSA^2. This was surprising because many anticancer agents are administered based on body surface area, while a dose requirement based on BSA^2 is unknown to Applicants and certainly extremely uncommon.

Applicants further devised new methodologies for some of the steps in the nomogram development process. For example, no established method was available to optimize accuracy of the predicted dose. Applicants accomplished this task by using computer simulations to identify the "ideal dose" that would give the precisely desired plasma concentration at 48 hours. A comparison of this "ideal dose" with the actual results in patients led to the introduction of a correction factor that improved the accuracy of the nomogram predictions by 12%. The above composite findings then were used to develop the suramin dosing nomogram. The innovativeness and enablement of the nomogram are indicated by its success in finding the proper suramin dose to maintain the desired plasma concentrations in 94% of treatments, in spite of the substantial inter-patient variability.

As the foregoing shows, the instant disclosure is based on unexpected and surprising findings made after substantial experimentations in experimental animals and in human patients. Finally, the substrate suramin in the kit cannot be used to provide a personalized treatment to a patient in accordance to said patient's characteristics without the printed matter. Likewise, the intended use of the printed instruction, *i.e.*, calculating the suramin dose to be given to a patient in accordance to said patient's personal characteristics, can only be practiced when the suramin is contained in the same kit.

Conclusion

In view of the claim amendments and remarks submitted herewith, allowance of the claims and passage to issue of this application respectfully is requested. If an allowance of the claims is not forthcoming, please provide Applicants an opportunity for a telephone interview.

Respectfully submitted,

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